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A facile one-pot procedure for the transformation of acetonides into diacetates catalyzed with $Bi(OTf)_3 \cdot xH_2O$

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Abstract

The transformation of acetonides into the corresponding diacetates is often required in the synthetic chemistry. An efficient procedure for direct conversion of acetonides into diacetates in the presence of $Bi(OTf)_3 \cdot xH_2O$ under mild conditions has been developed. Primary hydroxyl-acetonides could be selectively transformed into diacetates in the presence of anomeric acetonides and the anomeric acetonides could be tunably converted into 2-acetoxyisopropyl or diacetate groups.

Keywords: Acetal; Acetate; Acetonide; Homogeneous catalysis; Protecting groups

1. Introduction

The acetonide is one of the most frequently used protecting groups in synthetic chemistry because they are readily introduced and removed, as well as they are considerably stable under most reaction conditions.[1] As an efficient protecting group for vicinal diols, isopropylidene group has also been extensively employed in carbohydrate chemistry,[2] nucleoside[3] and polyhydroxy compound chemistry.[4] This group is acid and Lewis acid sensitive while it survives under strongly basic conditions, for example, alkyl lithium reagents, metal hydride reduction and catalytic hydrogenation reactions. On the other hand, acetates are also frequently employed to mask hydroxy groups and with typical characteristics of base-lability and acid-stability.[5] Therefore, as protecting groups, both acetonides and acetates are complementary in stability and sensitivity under acid- and base-conditions. Practically, the transformation of acetonides into diacetates is frequently encountered and employed in synthetic chemistry, particularly, in the synthesis of carbohydrates and nucleosides.[6]

To the best of our knowledge, the methods documented for accomplishing this transformation involved two steps: first, the removal of isopropylidene groups and subsequently, acetylation with acetic anhydride. For example, treatment with 80% AcOH first and followed by Ac_2O–pyridine;[7] treatment with 6 M H_2SO_4 in dioxane at 100 °C for 2 h and then with AcOH, Ac_2O–H_2SO_4 at rt for 10 h;[8] or TFA first and followed by Ac_2O–pyridine.[9] Huang and Bobek[10] reported a method to convert 1,2-isopropylidene of glucofuranose derivatives into corresponding 1-acetoxy-2-benzoyloxy derivatives via the cleavage of isopropylidene acetal with iodine–methanol and subsequent benzoylation and acetylation, respectively. Herein, we wish to report an efficient method for the direct conversion of acetonides into corresponding diacetates.

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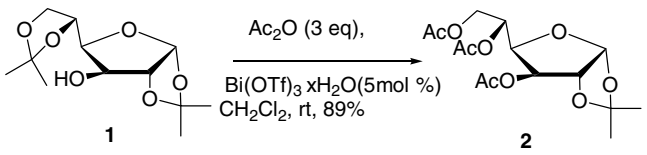
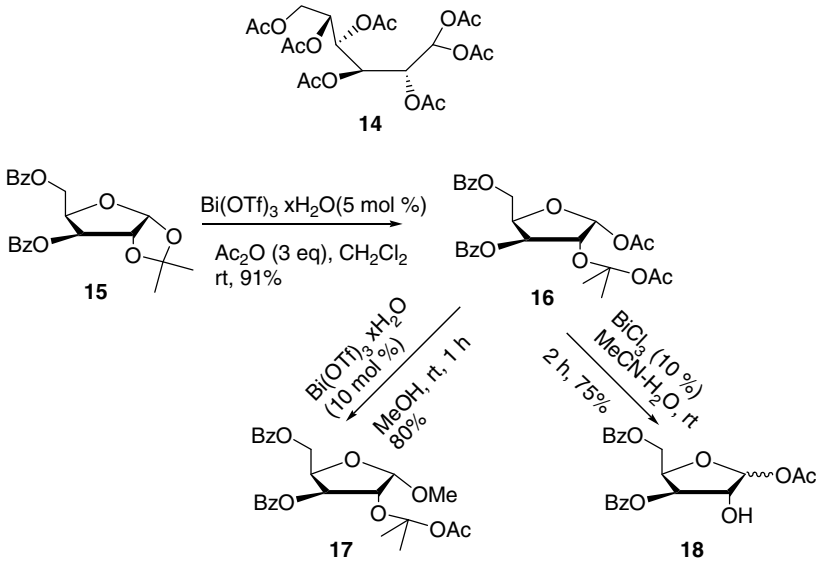


2. Results and discussion

In the course of our continuous research in the synthesis of nucleosides, the treatment of glucose diacetonide **1** with acetic anhydride at room temperature in the presence of $Bi(OTf)_3{\cdot}xH_2O$ (5 mol %) in CH_2Cl_2 generated the triacetyl product **2** in 89% yield. Furthermore, $Bi(OTf)_3$ has been widely employed in organic synthesis recently.[11] This interesting result prompted us to examine the scope of this direct transformation protocol. More sugar acetonides were prepared and treated with Ac_2O (3.0 equiv) under similar reaction conditions. As for all glucose diacetonide **1**, **3**, **5** and **6** and xylose derivatives **8**, it can be seen as shown in Table 1, the primary hydroxy acetonides were selectively converted into relative diacetates with excellent yields in the presence of the anomeric acetonide under this one–pot reaction conditions (Table 1, entries a–e). In addition, the anomeric isopropylidene groups could not be substituted by acetyl groups even though more Ac_2O was added and reaction time was extended, which showed how selective this reaction was under these mild conditions. As anticipated, mannose diacetonide **10** was selectively transformed into triacetates **11** in 91% yield. The anomeric benzoate was also displaced by acetate group (Table 1, entry f) with the inversed configuration of 1-C. However, direct transformation of the anomeric acetonides into diacetates is quite valuable in the synthesis of nucleosides in view of the common synthetic methods for nucleosides.[12] Therefore, monoacetonide sugar derivatives **12** and **13** were treated with Ac_2O (10 equiv) under the same reaction conditions as mentioned above to be expected to give the corresponding acetates. As the matter of fact, these isopropylidene groups were maintained intact and only hydroxyl groups were acetylized to give diacetate **9** and triacetate **2** (Table 1, entries g and h), respectively. Other Lewis acids were employed as substitutes for $Bi(OTf)_3{\cdot}xH_2O$ to be expected to induce direct transformation. However, no satisfactory result was obtained under various conditions. For instances, $BiCl_3$ and $InCl_3$ led to no product at all; **13** was converted into an unexpected product **14** with $FeCl_3$ and $AlCl_3$ as catalysts and BF_3 etherate led to the expected products in neat Ac_2O with moderate yields.



Accordingly, 3,5-dibenzoyl acetonide **15** was subjected to this one-pot procedure. Undesired product **16** was obtained as an oil in 91% isolated yield, in which the isopropylidene group was partially transformed. The molecular structure was characterized by ^1H NMR, ^{13}C NMR and MS (ESI) spectra. In order to further elucidate the position of the 2-acetoxyisopropyl group, **16** was treated with absolute methanol in the presence of $Bi(OTf)_3{\cdot}xH_2O$ (10 mol %) at room temperature to give **17** in 80% yield rather than the desired product with the loss of 2-acetoxyisopropyl group. Besides the signals for the isopropylidene group, the resonance signal of anomeric proton (**17,** H-1) appeared upfield (δ 5.70) in contrast to the corresponding resonance signal (δ 6.33, H-1) for compound **16** in ^1H NMR spectra. In addition, neither **16** nor **17** was an α- and β-mixture but a pure isomer. To the best of our knowledge, this half cleaved anomeric acetonide **16** has never been documented and it is valuable in synthetic chemistry due to its lability to release hydroxyl group under mild conditions. In the solution of acetonitrile–H_2O with $BiCl_3$ (10 mol %) as the catalyst at room temperature, the 2-acetoxyisopropyl group in **16** was cleaved to form **18** in 75% yield, in which the –OH

Table 1
Selective transformation of acetonides into diacetates with $Bi(OTf)_3{\cdot}xH_2O$ (5 mol %) at rt

Entry	Substrate	Product[a]	Time (h)	Yield[b] (%)
a	**1** R = H	**2** R = Ac	2.5	89
b	**3** R = Ts	**4** R = Ts	2	83
c	**5** R = Ac	**2** R = Ac	1.5	90
d	**6** R = Bz	**7** R = Bz	1.5	88
e	**8**	**9**	1.5	88
f	**10**	**11**	1	91
g	**12**	**9**	2	92
h	**13**	**2**	3	91

[a] Characterized by ^1H NMR spectra.
[b] Isolated yields.

was the sole active function group. These results suggest that this one-pot procedure could be applied to the synthesis of 2′-modified nucleosides and nucleotides.[13]

Under these reaction conditions, xylofuranose derivatives **9**, **20**, **22** and **24** were also smoothly transformed into the corresponding products **19**, **21, 23** and **25** (Table 2, entries a, c–e), respectively. Similar results (Table 2, entries f–h) were also obtained as a number of anomeric acetonides, such as **2**, **4** and **7**, which were treated with Ac_2O and $Bi(OTf)_3{\cdot}xH_2O$ (5 mol %) in CH_2Cl_2 solution at room temperature. The structures of the products were all characterized with ^1H NMR, ^{13}C NMR and MS (ESI) spectra. Moreover, the stereoselective products would be quite useful for the stereoselective synthesis of nucleosides.

Since acyclic acetyloxyacetal might be more reactive than cyclic acetal, it would be possible to convert compound **26** into pentaacetyl glucofuranoside **29**. Therefore, a solution of 3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose **2**, Ac_2O (3 equiv) and $Bi(OTf)_3{\cdot}xH_2O$ (5 mol %) in dichloromethane was heated under reflux. Compound **26**, however, was still obtained as the main product with trace amounts of the expected product **29**. Finally, **29** (85%) was obtained in reflux CH_2Cl_2 solution with increasing amount of catalyst, $Bi(OTf)_3{\cdot}xH_2O$, by 15 mol % (Table 3, entry a), and **26** was also observed on TLC plate as an intermediate in this process. Additionally, **29** is an anomeric mixture rather than a single product. Under this one-pot reaction conditions, a number of anomeric acetonides, **4**, **7**, **9** and **15** (Table 3, entries b–e), were also directly converted into corresponding diacetates in good yields.

In conclusion, we have established a useful procedure for the direct transformation of the acetonides into the corresponding acetates efficiently under mild conditions, and this protocol has some advantages: excellent selectivity between the transformation of the primary hydroxyl-acetonides and anomeric acetonides; tunable transformation of anomeric acetonides into relative diacetates or acyclic acetonides. The application of this protocol to the synthesis of nucleosides and carbohydrates is underway in our laboratory and the results will be reported in the due course.

3. Experimental

All the conversion reaction were carried out at least twice to ensure reproducibility.

3.1. Typical synthetic procedure

$Bi(OTf)_3{\cdot}xH_2O$ (0.05 or 0.15 mmol) was added to a solution of substrate (1.0 mmol) and Ac_2O (0.27 mL, 3.0 mmol) in CH_2Cl_2 (5 mL), and stirred at rt (for the products listed in Tables 1 and 2) or under reflux (for the products listed in Table 3). After complete conversion, saturated aqueous solution of $NaHCO_3$ (10 mL) was added. The aqueous solution was separated and extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was isolated through short column chromatography on silica gel.

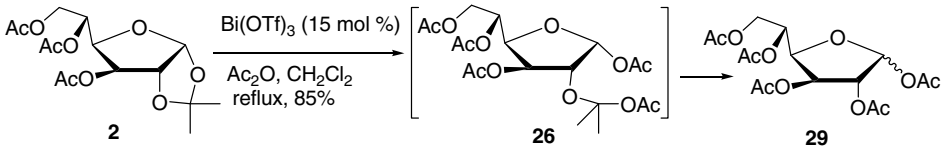
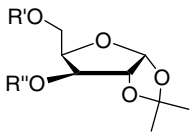
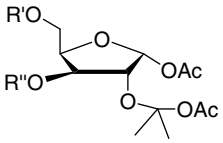
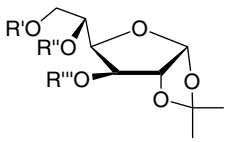
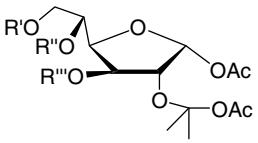
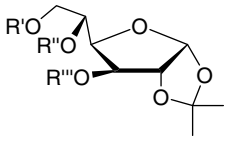
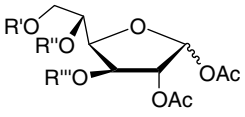
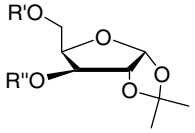
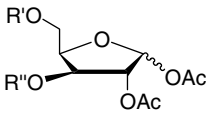


Table 2
Unexpected products in the transformation of anomeric acetonides

Entry	Substrate	Product[a]	Time (h)	Yield[b] (%)
				
a	**9** R′ = R″ = Ac	**19** R′ = R″ = Ac	3	91
b	**15** R′ = R″ = Bz	**16** R′ = R″ = Bz	2.5	91
c	**20** R′ = Bz, R″ = *p*-Ts	**21** R′ = Bz, R″ = *p*-Ts	2	92
d	**22** R′O = H, R″ = Bz	**23** R′O = H, R″ = Bz	2.5	88
e	**24** R′ = R″ = Bn	**25** R′ = R″ = Bn	0.5	83[c]
				
f	**2** R′ = R″ = R‴ = Ac	**26** R′ = R″ = R‴ = Ac	4.5	85
g	**4** R′ = R″ = Ac, R‴ = *p*-Ts	**27** R′ = R″ = Ac, R‴ = *p*-Ts	3.5	87
h	**7** R′ = R″ = Ac, R‴ = Bz	**28** R′ = R″ = Ac, R‴ = Bz	2.5	86

[a] Characterized by ^{1}H NMR, ^{13}C NMR (ARX 400 MHz and 100 MHz) and MS spectra.
[b] Isolated yields.
[c] $Bi(OTf)_3 \cdot xH_2O$ (3 mol %).

Table 3
Direct transformation of anomeric acetonides into acetates

Entry	Substrate	Product[a]	Time (h)	Yield[b] (%)
				
a	**2** R′ = R″ = R‴ = Ac	**29** R′ = R″ = R‴ = Ac	5	85
b	**4** R′ = R″ = Ac, R‴ = *p*-Ts	**30** R′ = R″ = Ac, R‴ = *p*-Ts	5.5	85
c	**7** R′ = R″ = Ac, R‴ = Bz	**31** R′ = R″ = Ac, R‴ = Bz	6.5	87
				
d	**9** R′ = R″ = Ac	**32** R′ = R″ = Ac	6.5	82
e	**15** R′ = R″ = Bz	**33** R′ = R″ = Bz	6	86

[a] Characterized by ^{1}H NMR spectra (ARX 400 MHz).
[b] Isolated yields.

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